Antipsychotics

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náhled|100mg tiapridal in an ampule

Antipsychotics (previously also referred to as *neuroleptics*) are drugs intended primarily for the **treatment of psychoses** – diseases manifested by disorders of thinking (delusions) and perception (hallucinations). As medications of second choice, they can be used for bipolar affective disorders, or unamanageable anxiety, depression, or to suppress agitation, aggression, and psychomotor restlessness. Antipsychotics act primarily as dopamine receptor antagonists.

We divide them into two or three generations:

- 1st generation, the so-called **classic** or **typical** (previously referred to as neuroleptics) – they have a strong sedative effect, but they might not be effective enough in the treatment of negative symptoms and are also characterized by serious **side effects** arising from the blockage of dopaminergic neurons in the extrapyramidal pathways;
- 2nd generation, the so-called **atypical antipsychotics** – extrapyramidal side effects are minimal, they work in therapy of negative symptoms (autism) and are suitable for maintenance therapy (schizophrenia).
- 3rd generation, so-called **dopamine system stabilizers** - the newest substances (aripiprazole, brexpiprazole) act as partial D_2 receptor agonists, stabilizing the mesolimbic dopaminergic system. They do not have extrapyramidal side effects and do not cause hyperprolactinemia. Sometimes, they are classified in a separate third generation, other times they are classified as the second one.

Classic antipsychotics

Mechanism of action

The basis of the effect is the **blockade of receptors** and r**eduction of neurotransmitter effect** on the CNS. **Dopamine** and partially **serotonin** receptors antagonism is the most important for their effect. The classic antipsychotics also have an antagonistic effect on noradrenaline, acetylcholine, or histamine receptors, but this mostly causes side effects.

thumb|300 px|Dopaminergic systems thumb|300px|Dopamine involvement in the basal ganglia circuit
Antipsychotics in the CNS integrate with **three dopaminergic systems**:

- mesolimbic,
- nigrostriatial and
- tuberoinfundibular.

An interaction of the neurons of the **mesolimbic** system is important for the **antipsychotic effect**, the others are more responsible for side effects. Disruption of the **nigrostriatial** pathways leads **to motoror effects** (tremor, hypertonic-hypokinetic syndrome) − **parkinsonisms**. When the **tuberoinfundibular** neurons are blocked, there are unwanted vegetative effects − disruptions of the menstrual cycle. The D_2 receptors are the most important for the antipsychotic effect− substances with the greatest affinity for them are the most effective. (Dopaminergic systems and the function of dopamine are portrayed by the pictures 'Dopaminergic systems' and 'Dopamine involvement in the basal ganglia circuit' in this article.)

Effects

Mental and motor **depression útlum** (apathy, drowsiness, reduced initiative), lowers aggression and restlessness.

Side effects

Due to their low selectivity, classic antipsychotics tend to have many side effects, which result from the blockade of a number of receptors.

Blockade of α_1 - orthostatic hypotension, erectile dysfunction,

Muscarinic receptor blockade - dry mouth, dry mucous membranes, ucho v ústech, suchost sliznic, accommodation disorder, urinary retention, constipation,

Blockade of dopamine receptors of the basal ganglia - extrapiramidal side effects: **parkinsonism**, acute dyskinesia, tarditive dyskinesia, akathisia,

Histamine receptors blockade - sedation.

Pharmacokinetics

Bioavailability after oral administration tends to be low, especially with chopromazine, lemomepromazine. When it comes to dosage, there are big differences in the doses for individual patients. For a fast onset effect, we choose an i.v. application. For a long-term maintenance treatment, depot parenteral forms with an extended release (haloperidol, fluphenazine) can be chosen.

Elimination half-lives tend to be moderate to **long** (10–35 hrs.) and the metabolites of antipsychotics tend to be effective as well.

The volume of distribution is usually large and it takes a long time to reach a steady state concentration.

Representatives

Classic antipsychotics are divided according to their effect into

- **sedative** (chlorpromazine, levomepromazine, chlorprothixen, flupenthixol, zucopenthixol) and
- **incisive** (haloperidol, melprenone, fluphenazine).

Less practical is the division based on chemical structure into

- phenothiazines (chlorpromazine, levomepromazine, fluphenazine),
- thioxanthenes (chlorprothixene, flupenthixol, zuclopenthixol) and
- butyrophenones (haloperidol, melprenone).

thumb|150px|chemical structure of haloperidol thumb|150px|haloperidol ester – depot haloperidol decanoate

Sedative

chlorpromazine
: the first antipsychotic introduced into practice in 1952, it meant a breakthrough in the therapy of psychosis – it enabled pharmacotherapy, it is still used today, i.v. for the management of acute attacks, for the therapy of hiccups

levomepromazine
: has a calming effect − aggressive patients, also has a hypotonic effect - insomnia, in trigeminal neuralgia

chlorprothixene
: characteristics similar to levomepromazine - sedative effect

flupenthixol
: for the treatment of schizophrenia and depression, p.o. and depot i.m. administration

zuclopenthixol

Incisive

Have a strong antipsychotic effect (strong D_2 antagonists), they have significant extrapyramidal effects, but a weaker sedative effect (only weak H_1 antagonists).

haloperidol
: very frequently used, lower risk of side effects (anticholinergic, orthostatic hypotension)

melperone
: *indication:* behavioral disorders in old age - restlessness, confusion

fluphenazine
: frequent depot administration in the form of decanoate for the maintenance trherapy of schizophrenia

Atypical antipsychotics

They have a **lower incidence of side effects**, especially extrapyramidal (hence atypical), but also cardiovascular or sexual dysfunction. Their **therapeutic spectrum is wider** as well. It includes the therapy of both positive symptoms (hallucinations, delusions, disorganized thinking, aggressiveness, agitation) and **negative** (autism, hypobulia, emotional and affective flatness). They are also efficient in patients, where therapy with classic antipsychotics did not lead to an improvement of their condition.

Mechanism of effect

They affect a **different spectre of neurotransmitters** than classic antipsychotics. Their effect of the striatum is lower compared to the classic antipsychotics, same as their affinity for D_2 receptors. Some block serotonin ($5\text{-}HT_2$) receptors more than dopamine receptors. **The blockade of 5-HT receptors** then leads to a reduction of the inhibitory effect on the dopaminergic system, which lead to the **suppression of the negative symptoms** of psychoses.

Pharmacokinetics

Elimination half-lives are moderately long (6–12 hrs.), distribution volumes are small. The pharmacokinetic parameters for atypical antipsychotics **often differ** from drug to drug, since the structures of their molecules also differ.

Classification

So far, they are divided **based on the effect on individual receptors**. The fact that each groups affects different receptors does not have a fundamental influence on their effectiveness or indication.

Selective antagonists of D_2, D_3 receptors

They antagonize **D_2, D_3** receptors **only**, they have a low occurrence of extrapyramidal effects, can cause hyperprolactinemia

sulpiride
: in lower doses, it affects negative and depressive symptoms, in higher doses, it affects positive symptoms, it also has a prokinetic effect, absorption after p.o. application is low, can cause hyperprolactinemia, *indication:* schizophrenia, depressive disorder, psychomotor restlessness

amisulpride
: *indication:* treatment of schizophrenia, dysthymia

thiapride
: *indication:* behavioral disorders in old age, aggression, chronic algic states

SDAs (serotonin and dopamine receptors antagonists)

thumb|200px|Risperidone – injection form thumb|200px|RISPOLEPT® tab. with risperidone They primarily block **dopamine, serotonin, and α_1 adrenergic** receptors.

Side effects tend to be mild and similar in all representatives - headaches, sedation, tachycardia, prolongation of the QT interval, orthostatic hypotension, erectile dysfunction, hyperprolactinemia, weight gain

risperidone
: one of the most frequently used atypical antipsychotics, even for negative symptoms of schizophrenia, *indication:* psychoses of all kinds, manic bipolar affective disorder, behavioral disorders, aggression, autism

paliperidone
: *indication:* therapy of schizophrenia, also available in depot form as paliperidone palmitate

ziprasidone
: has an antidepressant effect as well, does not affect body weight, *indication:* schizophrenia, bipolar affective disorder

sertindole
: significantly prolongs the QT interval

MARTA (multireceptor antagonists – multi acting receptor targeting antipsychotics)

Antagonize **dopamine, serotonin, α_1 adrenergic**, but even histamine and muscarinic receptors.

clozapine
: works also in patients who do not respond to treatment with other antipsychotics, in 1–2 % of cases, **agranulocytosis** is present- complete blood count check is necessary, side effects are not extrapyramidal, but side effects from blockade of α_1 , muskarinic, and histamine receptors are significant– orthostatic hypotension, fatigue, increase in body weight

olanzapine
: the spectre of receptor effect is similar to clozapine, but there is no risk of aganulocytosis, *side effects:* fatigue, weight gain, *indication:* schizophrenia, mixed bipolar disorder, *risks and contraindications:* age above 75, dementia, Parkinson's disease

quetiapine
: also acts as an antidepressant, reduces cognitive deficit, *side effects:* somnolence, orthostatic hypotension, increase in weight, indication: schizophrenia, bipolar affective disorder

zotepine
: *side effects:* somnolence, increase in weight

Other substances - 3rd generation antipsychotics

They are the so-called **dopaminergic stabilizers**, they act as a partial agonist of the D_2 receptors. They do not increase prolactin levels and have minimal extrapyramidal effects.

aripiprazole
partial D_2, D_3 agonist, 5-HT blocker, well tolerated, *side effects:* fatigue, nausea, akathisia

brexpiprazole
indication: schizophrenia, depressive episodes, *side effects:* upper respiratory tract infection, akathisia, increase in body weight, *metabolism and drug interaction:* it is a substrate of CYP2D6 and CYP3A4

Clinical use of antipsychotics

Indication

Antipsychotics are of irreplaceable significance in **psychiatric indications**:

- **psychotic disorders** – schizophrenic and schizoaffective disorders – their use requires experience, it is complex
- **agitation, aggressiveness** – parenteral haloperidol or levomepromazine
- **anxiety and other disorders** – also behavioral disorders, dementia – lower doses

They can also be used in **non-psychiatric** indications such as:

- **antiemetics** – in low doses, **haloperidol** – vomiting after opioids, **tiethylperazine** - antiemetics after vomiting of all sorts (previously a typical antipsychotic, not used in psychiatry today)
- **hypnotics** – levomepromazine in unmanageable insomnia
- **in anesthesiology** – neuroleptanalgesia
- **in neurology** – hypotonic-hyperkinetic type disorders (Huntington's disease)

Side effects

Those resulting from a blockade of specific receptors can be easily predicted - they are summarized in the following table:

Predictable side effects of antipsychotics

Blocked receptor	Effect
dopamine	extrapyramidal symptoms, endocrine disorders
α_1	orthostatic hypotension, dizziness, stuffy nose, sexual dysfunction (decrease of libido, impotence, delayed ejaculation), increased appetite
muscarinic	dry mouth, constipation, decreased micturition, mydriasis, blurred vision, tachycardia, confusion
H_1	fatigue, anti-inflammatory effect, increase in weight
5-HT_2	contribute to an antipsychotic effect (?), attenuation of aggression (?)

Other, unpredictable, are rare, but serious:

- **neuroleptic malignant syndrome** − fever, muscle rigidity, impaired consciousness, life-threatening
- **agranulocytosis**

Contraindications

Relative:

- comatose states
- **intoxication with sedative substances** − ethanol, barbiturates

Absolute:

- **Parkinson's disease**
- **neuroleptic malignant syndrome**
- **disorders of hematopoiesis**
- **glaucoma** − in antipsychotics with anticholinergic effect
- **prostate hypertrophy and conditions with worsened intestinal passage**

Interactions

- **antiepileptics** − reduction of effect
- **drugs prolonging the QT interval** – increased risk of ventricular arrhythmias
- **blood pressure lowering drugs**
- **anticholinergics**
- **tricyclic antidepressants** – increase in concentration by blocking the metabolism

References

Related articles

- Psychotropic drugs
- Neuroleptics (pediatry)
- Schizophrenia

Used literature

- LINCOVÁ, Dagmar – FARGHALI, Hassan. *Základní a aplikovaná farmakologie.* 2. edition. Galén, 2007. ISBN 978-80-7262-373-0.

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